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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,198	ZAPATA, GERARDO	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *May 26, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *8,9 and 26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/25/04; 6/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-29 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election of Group I (Claims 1-25) and species to aspartyl protease and Chinese hamster ovary cells in the reply filed on May 26, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8, 9 and 26-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected subject matter, there being no allowable generic or linking claim.

Claims 1-7 and 10-25 with species to aspartyl protease and Chinese hamster ovary cells are all the claims under examination.

Information Disclosure Statement

3. The U.S. patent references and non-patent literature references cited in the IDSs of June 25 and 26, 2004 have been considered and made of record.

Specification

4. The abstract and page 2 of the specification are objected to for including the attorney docket no. Each sheet of the specification shall contain no other information (see 37 CFR 1.171 (f)).

Appropriate correction is required.

5. The use of the trademarks (e.g., XenoMouse™) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

6. Claim 11 is objected to for being drawn for non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for the recitation "adjusting the conditions of the cell media"

as it is unclear whether in the adjusting step a) a proteolytic enzyme is added to the culture medium containing the expressed antibody, b) culture medium comprising an endogenous enzyme is added to the culture medium containing the antibody, c) culture medium containing the antibody is removed from the cells and chemically modified before the addition of culture medium containing an enzyme, or d) a critical time period for enzyme activation and completion of digestion is required.

8. Claim 12 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

a. It is unclear if a cell line having the exact biological properties and chemical identity of CHO-DG44 is known and publicly available, or can be reproducibly isolated without undue experimentation. A source of the CHO-DG44 cell line is disclosed at p. 14 [0048] of the specification, but there is no evidence or any assurance that the cell line is available to the public. The Examiner's "All Collections" search of the ATCC website for the CHO-DG44 cell line did not reveal any deposits under this name (see attached copy of search output). However, in cross-referencing the Examiner's PubMed search for this cell line with the ATCC website, the CRL-9096 clone for a dhfr deficient CHO cell line was identified (see copy of ATCC search output). Applicants are requested to clarify and provide assurances that the instant claimed CHO-DG44 cells

are biologically and/or chemically similar to the CRL-9096 clone. Otherwise, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the claimed cell line is an unpredictable event.

b. For example, "CHO cell are known to have very unstable karyotype due to chromosome rearrangements arising from translocations and homologous recombination, especially in response to amplification procedures" (Barnes et al. Biotech & Bioeng. 81:631-639 (2003); p. 632, Col. 2, ¶2). Therefore, it would require undue experimentation to reproduce the claimed CHO-DG44 cell line. Deposit of the cell line would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in

order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to

corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3-7 and 10-18 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using Fab, Fab', $F(ab')_2$, Fv and single chain antibodies that compete with the intact antibody for specific binding, does not reasonably provide enablement for making or using just any antibody fragments that do not retain binding activity or which cannot be used in immunoassays, immunotherapeutics or immunodiagnostics. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

The claims 1, 3-7 and 10-18 are drawn to producing any antibody fragment from any antibody produced into the culture medium by an antibody-producing cell line such as CHO-DG44, the steps of which involve "adjusting the conditions of the culture medium" to activate an antibody-cleaving enzyme in the medium such as an aspartyl protease by adjusting the temperature and the pH to about 3.5, inactivating an endogenous enzyme such as cysteinyl enzyme by pH adjustment prior to activating an aspartyl enzyme, substantially purifying antibody fragments by affinity chromatography, and a culture media comprising protein free media, a peptone source or CD-CHO media.

The specification specifically teaches general methods for generating binding fragments of an antibody including Fab, Fab', $F(ab')_2$, Fv, and single-chain antibodies [0016] by activating endogenous enzymes in the cell culture medium that are secreting the antibodies [0012] and enzymatic digestion of the secreted antibodies by aspartyl proteases, cysteinyl proteases, or a combination of both types of proteases by lowering the pH of the cell media to about pH 3.5 and adjusting the temperature to about 37°C, inhibiting the enzyme activity upon completing digestion (Example 1- demonstrates specific aspartyl enzyme digestion of antibodies), followed by the purification of the digested fragments (Example 2- demonstrates specific purification of

F(ab)2 fragments by chromatography steps) [0013]. The specification fails to enable antibody fragments as broadly claimed, which encompasses oligopeptides, peptides, etc., that would bind the specific antigen or ligand as the parent antibody.

Claim 1 recites "antibody fragments" and it is unclear what the scope of the fragments is intended. Do the fragments retain antigen or ligand binding activity, comprise oligopeptides falling within a given range of sizes, possess blocking activity (e.g., Fc fragment blocking full antibody binding), etc.? The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 79:1979). Rudikoff et al. teach that the alteration of a single amino

acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fragments of antibodies as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function. The specification defines the binding characteristics for the inventive antibody fragments discussed supra. The specification provides no direction or guidance regarding how to produce antibody fragments having the same binding specificity as the native or full antibody as broadly defined by the claims or what fragments would confer specific binding. The "antibody fragments" encompassed by the claims read broadly on as small as 2 amino acids, single CH1 or CH2 domains, Fc domains, etc. Furthermore, the specification does not even teach any utility for just any of these fragments insofar as how they can be used (MPEP 2164.01(c); In re Johnson 283 F.2d 370, 373 (CCPA 1960) or In re Brana, 51 F.2d 1560, 1566 (Fed. Cir. 1993)). Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the broadly claimed invention, the lack of predictability in the art as evidenced by Rudikoff et al and lack of guidance in the specification with regard to producing any antibody fragment having antigen-binding activity as that of the parent antibody, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1-7, 10, 11, 13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takai et al. (Biosci. Biotechnol. Biochem. 65:1082-1089 (2001); hereinafter referred to as "Takai") in view of Parham (J. Immunol. 131:2895-2902 (1983); cited in the IDS of July 26, 2004; hereinafter referred to as "Parham").

Claims 1-7, 10, 11, 13 and 16-18 are drawn to producing any antibody fragment from any antibody produced into the culture medium by an antibody-producing cell line such as CHO, the steps of which involve "adjusting the conditions of the culture medium" to activate an antibody-cleaving enzyme in the medium such as an aspartyl protease by adjusting the temperature and the pH to about 3.5, inactivating an endogenous enzyme such as cysteinyl enzyme by pH adjustment prior to activating an

aspartyl enzyme, substantially purifying antibody fragments by affinity chromatography, and a culture media comprising protein free media.

Takai discloses CHO cells transfected with constructs for expressing anti-human FcεRIα Abs (p. 1083, Col. 2, ¶5- p. 1084, Col. 1, ¶2), secretion of the Abs into serum-free media (p. 1084, Col. 1, ¶2; Figure 2A), isolating the secreted antibody and digesting with papain to generate Fab fragments (p. 1084, Col. 1, ¶4 to Col. 2, ¶1), affinity purifying Fab fragments on a HiTRAP CM Sepharose column (p. 1084, Col. 2, ¶2; Figure 3A). Takai discloses that "purification of a recombinant Ab from serum-containing medium is complex. Therefore, a serum-containing medium is not suitable for large-scale production" (p. 1086, Col. 2, ¶1); whole Ab was digested by immobilized papain and the digest contained Fab, Fc, and various other peptide fragments, and various conditions were examined for removal of the Fc and other fragments from the Fab fragment (p. 1087, Col. 1, ¶3- Col. 2, ¶1). Takai does not disclose enzymatic digestion of an antibody with an aspartyl protease such as pepsin. Because of the indefiniteness of Claim 1 as discussed, supra, and the use of "comprising" language, "adjusting the conditions of the cell media" is encompassed by addition of a proteolytic enzyme to the antibody for cleavage into fragments. Parham rectifies this deficiency in its disclosure.

Parham discloses that papain cleavage of antibodies into $F(ab)_2$ fragments has its drawbacks (p. 2895, Col. 2, ¶2); $F(ab)_2$ fragments can be generated directly from IgG1 in cell culture supernatants with addition of pepsin for treatment at pH 3.5 for 48 hr at 37°C (p. 2897, Col. 1, ¶2 to Col. 2, ¶2); adjusting acidification and neutralization of

the sample by addition of acid or base (p. 2897, Col. 1, ¶2); binding $F(ab)_2$ fragments to DE-52 column and elution (p. 2897, Col. 2, ¶1); pepsin digestion of IgG2a (p. 2898, Col. 1-2) and of IgG2b (p. 2898, Col. 2 to p. 2900, Col. 2, ¶1) at pH ranges of pH 4.0- 4.5 for IgG2a and pH 4.5-5.0 for IgG2b.

It would have been *prima facie* obvious to have produced the instantly claimed methods in view of Takai and Parham.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed method in view of Takai and Parham because Takai discloses producing antibodies in culture media from CHO cells and the steps of enzymatic cleavage of the antibody into a fragment by adjusting the pH and temperature and further purifying the fragment by affinity chromatography, and Parham teaches away from using papain to obtain a F(ab)2 fragment but instead discloses using an aspartyl enzyme, pepsin, in digesting three antibody isotypes, IgG1, IgG2a and IgG2b in cell culture media. Both Takai and Parham combined appreciate and disclose adjusting pH and temperature for modulating the cysteinyl (papain) and aspartyl (pepsin) enzyme activities to obtain desired digested antibody fragments. The technique of regulating cystenyl and aspartyl enzyme activities of antibody-containing culture supernatants by adjusting pH and temperature was well within the skill of the ordinary artisan at the time of the invention, and one could have been reasonably assured of success in doing so by combining the disclosures of Takai and Parham based on the

explicit and implicit disclosures. Thus the claims were *prima facie* obvious at the time of the invention in view of Takai and Parham.

11. Claims 1, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takai and Parham as applied to claim 1 above, and further in view of Zhang et al (Cytotechnology 16:147-150 (1994); hereinafter referred to as "Zhang") and Schifferli et al. (Focus 21:16-17 (1999); hereinafter referred to as "Schifferli").

The interpretation of Claim 1 is discussed supra. Claim 14 is drawn to media comprising peptone source and Claim 15 is drawn to CD-CHO media.

The interpretation of Takai and Parham is discussed surpa. Neither Takai nor Parham disclose media comprising a peptone source or CD-CHO media for the method step of culturing cells. Zhang and Schifferli rectify these deficiencies in their disclosures.

Zhang discloses that adding peptone to hybridoma medium can boost the level of antibody production and Schifferli discloses that CD-CHO medium is optimized for growth and expression of recombinant proteins by transfected cells.

It would have been *prima facie* obvious to have produced the instantly claimed methods in view of Takai and Parham and further in view of Zhang and Schifferli.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed method in view of Takai and Parham and further in view of Zhang and Schifferli because increasing the level of antibody production by the antibody-producing cell line of the instant claimed method by optimizing the culture

conditions using a peptone comprising medium of Zhang or the CD-CHO medium of Schifferli would have been well with ordinary skill at the time of the invention. One of ordinary skill would have been motivated to have combined the media reagents into the methods disclosed by Takai and Parham in order to maximize antibody production in order to generate antibody fragments in usable amounts. Also, because these reagents were commercially available, one could have readily obtained the materials at the time of the invention. One of skill in the art could have successfully combined the reagents into the methods of Takai and Parham as the media had been shown to be useful for expressing recombinant proteins including antibodies. Thus, the claims were *prima facie* obvious at the time of the invention in view of Takai and Parham and further in view of Zhang and Schifferli.

12. Claims 19, 21, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takai et al. (Biosci. Biotechnol. Biochem. 65:1082-1089 (2001); hereinafter referred to as "Takai") in view of Parham (J. Immunol. 131:2895-2902 (1983); cited in the IDS of July 26, 2004; hereinafter referred to as "Parham").

Claims 19, 21, 24 and 25 are drawn to methods for generating $F(ab)_2$ fragments from any antibody produced into the culture medium by an antibody-producing cell line, the steps of which involve "adjusting the conditions of the culture medium" to activate an antibody-cleaving enzyme in the medium such as an aspartyl protease by adjusting the pH, inactivating an endogenous enzyme such as cysteinyl enzyme by pH adjustment

prior to activating an aspartyl enzyme, substantially purifying antibody fragments by affinity chromatography.

See the interpretation of Takai and Parham as discussed supra.

See the discussion regarding the obviousness of combining the disclosures of Takai and Parham and the assurance of success in doing so as discussed supra at the time of the invention in order to obtain the instantly claimed method for generating $F(ab)_2$ fragments from a culture medium treated via activation of aspartyl enzyme.

13. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takai and Parham as applied to claim 19 above, and further in view of Schifferli.

The interpretation of Claim 19 is discussed supra. Claim 20 is drawn to CD-CHO media.

The interpretation of Takai and Parham is discussed supra. Neither Takia nor Parham disclose CD-CHO media for the method step of culturing cells. Schifferli rectifies this deficiency in its disclosure.

The interpretation of Schifferli is discussed supra.

See the discussion regarding the obviousness of combining the disclosures of Takai, Parham and Schifferli and the assurance of success in doing so as discussed supra at the time of the invention in order to obtain the instantly claimed method for generating $F(ab)_2$ fragments from a culture medium such as CD-CHO.

14. Claims 19, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takai and Parham as applied to claim 19 above, and further in view of Mason et al. (Protein Expression and Purification 23:45-54 (2001); hereinafter referred to as "Mason").

The interpretation of Claim 19 is discussed supra. Claim 22 is drawn to inhibiting cysteinyl enzyme by adding an inhibitor to the medium and Claim 23 is drawn to the cysteinyl enzyme inhibitor, E64.

The interpretation of Takai and Parham are discussed supra. Neither Takai nor Parham disclose adding a cysteinyl enzyme inhibitor such as E64 to the medium. Mason rectifies this deficiency in its disclosure.

Mason discloses that E64 is a "generic cysteine proteinase inhibitor" (Abstract; p. 53, Col. 1, ¶2 and Col. 2, ¶1).

It would have been *prima facie* obvious to have produced the instantly claimed methods in view of Takai and Parham and further in view of Mason.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed method in view of Takai and Parham and further in view of Mason because increasing the level of $F(ab)_2$ production via aspartyl enzyme activity by reducing cysteinyl enzyme activity, which would otherwise generate Fab fragments, would have been obvious and within reasonable success to the ordinary skilled artisan. Optimizing the culture conditions using E64 would have been well with ordinary skill at the time of the invention. One of ordinary skill would have been motivated to have

combined the inhibitor into the methods disclosed by Takai and Parham in order to maximize $F(ab)_2$ production in order to generate fragments in usable amounts. Also, because E64 was commercially available, one could have readily obtained the material at the time of the invention. One of skill in the art could have successfully combined E64 into the methods of Takai and Parham as E64 was known to be a "generic cysteine proteinase inhibitor". Thus, the claims were *prima facie* obvious at the time of the invention in view of Takai and Parham and further in view of Mason.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER